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REVIEW ARTICLE

Sedation in the ICU

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Abstract

Sedation practices are key to improving intensive care unit (ICU) outcomes. Adequate treatment of pain, minimization of sedation, delirium prevention, and improved patient interaction to ensure early rehabilitation and faster ventilator liberation are evidenced-based components of ICU care. Here we review components of appropriate ICU sedation including the use of multicomponent care bundles such as the ABCDEF bundle with a focus on changes in ICU practice that followed the Covid-19 pandemic.

C. Corey Hardin, M.D., Ph.D., Editor

Introduction

The coronavirus disease 2019 (Covid-19) pandemic altered practice across medicine, but had a particularly lasting impact on critical care. During the pandemic, intensive care units (ICUs) experienced reduced contact between patients and clinicians, deeper sedation targets, increased utilization of neuromuscular blocking agents, and reduced family visitation.[1] In many ways these changes ran counter to what was considered good practice prior to the pandemic. The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the Intensive Care Unit (PADIS) laid out the key components of optimal management of critically ill patients and were adopted as standard practice prior to the pandemic.[2] According to these guidelines, analgesic agents should be utilized first, before sedatives, via a protocol that includes routine pain assessment with the Behavioral Pain Scale (BPS, scored from 1 to 4 in each of the three domains of facial expression, upper limb movement, and compliance with mechanical ventilation; higher scores indicate more pain) or Critical Care Pain Observation Tool (CPOT, scored from 0 to 2 in each of the three domains of facial expression, body movements, and muscle tension; higher scores indicate more pain). In patients requiring sedative agents to facilitate mechanical ventilation, clinicians should aim for light sedation using nonbenzodiazepine regimens with either propofol or dexmedetomidine. Patients should be regularly evaluated for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC). Lastly, although considered a conditional recommendation based on low-quality evidence, multicomponent bundles should be implemented. Various bundles have been reported in the literature and primarily focus on delirium prevention.[3-6] The ABCDEF bundle is widely utilized and includes Assessment, prevention, and management of pain; Both spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs); Choice of analgesia and sedation; Delirium assessment, prevention, and management; Early mobility and exercise, and; Family engagement and empowerment.[2,7]

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Since publication of the 2018 PADIS guidelines and the ABCDEF bundle, multiple studies have demonstrated positive impacts of bundle implementation on clinical outcomes, such as reductions in ICU length of stay and mortality, with an associated reduction in net health care costs.[8-12] Additionally, in studies evaluating bundle compliance, even small improvements resulted in a dose-dependent reduction in delirium, increase in coma-free days, and increase in hospital survival.[8,9] Most recently, Barr and colleagues evaluated the aggregate effects of bundle implementation on outcomes in mechanically ventilated patients and demonstrated reductions in ICU length of stay and days of mechanical ventilation.[8] Study hospitals had a high compliance rate for components "A" and "B" prior to the intervention period, but improvements in "C" and "D" were made with notably increased sedation assessments and delirium screening followed by associated reductions in the use of benzodiazepine infusions. Despite this, emerging evidence since the pandemic indicates that overall bundle compliance may be reduced compared with prepandemic levels.[1,13] The focus of this narrative review is to highlight the importance of evidenced-based sedation practices to ICU outcomes, including the use of such multicomponent bundles. We review the components of the ABCDEF bundle and highlight literature that has been published since the 2018 PADIS guidelines.

Assess, Prevent, and Manage Pain

The 2018 PADIS guidelines recommended utilizing analgosedation (analgesia-first or analgesia-only strategies ensure treatment of pain prior to the start of sedative infusions which do not treat pain) via a protocol-based assessment and treatment plan.[1] In a pooled analysis for the guidelines, protocolized analgosedation reduced the duration of mechanical ventilation and ICU length of stay, as well as reducing overall sedative requirements and reported pain intensity.[2,14] The recent NONSEDA trial compared an analgesia-only regimen with light sedation strategies but found no significant impact on mortality between groups.[15] Utilization of multimodal pharmacotherapy to minimize opioid use is recommended by the 2018 guidelines, although opioids remain the mainstay for pain management. At the time of guideline publication, data were lacking regarding optimal opioid selection.[2]

To investigate differences in opioid choice, the ANALGESIC trial evaluated ventilator-free days at 28 days in patients who received fentanyl- versus morphine-based analgosedation.[16] Use of fentanyl significantly increased the median number of ventilator-free days as compared with morphine; however, mechanical ventilation across trial groups was less than 2.5 days, limiting applicability to patients who require longer durations of support. In a retrospective cohort study, Choi and colleagues also evaluated ICU length of stay and duration of mechanical ventilation among patients who received fentanyl- versus hydromorphone-based analgosedation.[17] They identified no differences regarding ICU length of stay or duration of mechanical ventilation. The fentanyl group had a higher use of dexmedetomidine and lower use of chemical paralysis, potentially highlighting differences in severity of illness between the two groups. These studies support the concept that any opioid can likely be utilized if used in equianalgesic doses.

Ketamine is an adjunctive pain option highlighted in the PADIS guidelines, but data on its use are largely limited to postsurgical patients, with very low-quality evidence.[1] Ketamine has many favorable qualities including being less likely to cause hypotension, having analgesic properties, and potentially reducing opioid dosages.[18] That cumulative opioid doses may increase risk of delirium has led to an increasing body of research evaluating the use of ketamine in conjunction with opioids or as monotherapy.[16,19-24] Multiple studies have demonstrated a reduction in sedative and opioid consumption and improved time within goal sedation parameters as measured by the Richmond Agitation–Sedation Scale (RASS) of −1 to +1 with adjunctive ketamine use, although these outcomes are only surrogate outcomes.[19,21,22] Ketamine use was associated with reduced rates of SAT and SBT implementation in another study, leaving additional questions surrounding the impact of ketamine use within a critically ill patient population.[25]

Even with a growing literature aimed at identifying the optimal analgesic agent, there is currently not enough evidence to specify a first-line agent, and data regarding adjunctive analgesia remain of low-quality. Clinicians should continue to use clinical judgment, drug properties, and patient characteristics to develop analgosedation plans with titration using validated assessment tools. Additional research is needed to determine if analgesic selection impacts short- and long-term outcomes and to determine optimal multimodal analgesia strategies.

Both Spontaneous Awakening Trials and Spontaneous Breathing Trials

SATs and SBTs have been shown to reduce the duration of mechanical ventilation and hospital length of stay.[26] Both

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SATs and SBTs should be performed daily in mechanically ventilated patients meeting safety screen criteria. In patients who do not pass SATs or SBTs, sedation should be resumed at half the prior dose and re-titrated to achieve light sedation. Although daily sedation interruptions have become standard of care for mechanically ventilated patients, there remain barriers to consistent implementation. Balas and colleagues performed a secondary analysis from the ICU Liberation Collaborative database and demonstrated that patients who had a documented sedation target and received more frequent sedation level assessments were more likely to have an SAT and SBT performed the next day.[25] Additionally, patients receiving ketamine or benzodiazepines were less likely to have an SAT and SBT performed. Although a number of factors likely impact successful implementation of SAT and SBT, this study demonstrates that sedation practices play a key role. Given the benefits of daily awakening and breathing trials, sedation protocols should focus on minimizing modifiable factors that negatively impact implementation.

Choice of Analgesia and Sedation

The first step of selecting an analgesic and sedative agent is setting a goal sedation depth. In a pooled analysis included in the PADIS guidelines, lighter sedation strategies were associated with reduced time to extubation and rates of tracheostomy.[2] A recent meta-analysis showed reduced duration of mechanical ventilation, time to extubation, ICU and hospital length of stay, and ventilator-associated pneumonia associated with light sedation.[27] While the goal for most patients should be light sedation, the use of deeper sedation levels may be clinically appropriate in patients who are receiving neuromuscular blockade, have refractory ventilator asynchrony, or those receiving treatment for status epilepticus and refractory intracranial hypertension.

Utilizing deep sedation goals in patients with acute respiratory distress syndrome (ARDS) and Covid-19 offered many lessons. The COVID-SED study evaluated the impact of early, deep sedation during the first 48 hours of admission on in-hospital mortality.[28] Investigators found early and deep sedation was associated with longer duration of mechanical ventilation and higher mortality among patients with and without Covid-19, congruent to previously published data in a non–Covid-19 patient population.[29] Wongtangman and colleagues evaluated whether patients with Covid-19 and ARDS were at a higher risk of in-hospital mortality due to prolonged coma (defined as RASS ≤−3) than patients with non–Covid-19 ARDS.[30] In-hospital mortality was significantly increased in patients with coma, irrespective of sedative choice. Mediation analysis found that coma mediated 59% of in-hospital mortality and, notably, the impact of Covid-19 diagnosis on mortality was found to be insignificant.

Despite the evidence supporting the use of light sedation, clinicians may feel deeper sedation is required to control respiratory drive and minimize the potential for ventilator-induced lung injury caused by asynchrony. Evidence for this approach is conflicting.[31-33] Dzierba and colleagues recently demonstrated that sedation depth was not correlated with respiratory drive at any evaluation time, highlighting the multitude of factors that impact respiratory drive outside of sedation.[34] As an alternative to increasing sedation depth, investigators have evaluated the impact of adjusting ventilator settings by increasing inspiratory time or switching to pressure support ventilation when feasible, which reduced the breath-stacking asynchrony index.[35] Based on these data, a recent review proposed adding "R — control respiratory drive" to the ABCDEF bundle to emphasize that ventilator settings should be addressed before utilizing deeper sedation and neuromuscular blocking agents to avoid the negative outcomes associated with deeper levels of sedation.[36]

Once clinicians select goal sedation depth, they should balance the risks and benefits of analgesic and sedative agents, and utilize drug- and patient-specific parameters to select appropriate agents (Table 1). The PADIS guidelines recommend utilizing nonbenzodiazepines agents, either propofol or dexmedetomidine, as first line after the treatment of pain.[1] Although not the primary focus of this review, the numerous landmark trials supporting this recommendation are highlighted in Table 2.[37-40] There is no guideline consensus regarding the preferred nonbenzodiazepine agent. The MENDS2 trial was a randomized trial that evaluated dexmedetomidine versus propofol in achieving target sedation goals, and the impact on the number of days alive without delirium or coma during the 14-day intervention period.[41] Researchers found no difference in outcomes between these two agents when titrated to light sedation. The SPICE III randomized trial evaluated whether early use of dexmedetomidine versus usual care had an effect on all-cause mortality at 90 days.[42] This trial found no difference in mortality between groups and increased risk of hypotension and bradycardia with dexmedetomidine use. Based on these trials, there is currently no evidence to support one nonbenzodiazepine regimen over the other when targeting light levels of sedation. Clinicians should evaluate goal sedation depth and

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Table 1. Analgesia and Sedative Agent Key Characteristics.*

Agent	Typical Dose	Onset, Duration, Half-life	Pharmacokinetics, Metabolism, Elimination	Active Metabolite?	Additional Considerations
Analgesia — Opioid: Utilize bolus doses before continuous infusions					
Fentanyl	Intravenous push: 25–50 μg every 30 minutes as needed Infusion: 25–200 μg/hr	Onset: 1–2 minutes Duration: 30–60 minutes Infusion: context-sensitive half-life leads to increased duration of effect with prolonged infusion times	High first-pass clearance with approximately 75% excreted via urine as inactive metabolites. Hepatically metabolized via CYP3A4, reduced or increased elimination with CYP3A4 inhibitors or inducers, respectively; reduced elimination with heart failure, hepatic disease. Highly lipophilic with increased accumulation in patients receiving longer durations or in morbidly obese patients.	No	Chest wall rigidity/myoclonus reported with high doses or when quickly administered. Alterations in respiratory rate and alveolar ventilation may last longer than analgesic effect.
Hydromorphone	Intravenous push: 0.2–1 mg every 2–3 hours as needed Infusion: 0.5–2 mg/hr	Onset: 5–10 minutes Duration: 3–4 hours	Extensively metabolized via glucuronidation in the liver, with >95% metabolized to HM6G. Patients with hepatic disease may have increased exposure but does not preclude them from use. Glucuronidation is generally preserved with hepatic disease. Utilize lower initial starting doses with slower uptitration.	No	May cause histamine release leading to hypotension, pruritus, urticaria or flushing.
Morphine	Intravenous push: 2–4 mg every 1 hour as needed Infusion: 1–5 mg/hr	Onset: 5–10 minutes Duration: 2–4 hours	Metabolized via glucuronidation in the liver to M3G and M6G. Significantly altered in patients with renal and hepatic impairment. M3G/M6G are primarily excreted via the kidneys, prolonged half-life and accumulation with renal failure.	Yes/No M3G: inactive M6G: active — contributes significantly to analgesic effect of morphine	Increased likelihood of histamine release leading to urticaria, hives, hypotension. M3G effects with accumulation: neurotoxicity and myoclonus; M6G effects with accumulation: significant sedation and respiratory depression.
Analgesia — Adjunctive					
Ketamine	Infusion analgesia dosing: 1–5 μg/kg/min	Onset: 1 minute Offset: approximately 2 hours	Complex and extensive hepatic metabolism: CYP3A4, CYP2B6, CYP2C19 mediate N-demethylation into active metabolite norketamine.	Yes Norketamine	Emergence reactions may occur, typically with initiation/discontinuation and with periprocedural bolus doses. Use with caution in patients with psychiatric disorders. Use with caution in patients with uncontrolled hypertension or tachycardia.
Acetaminophen	Oral/Rectal: 650–1000 mg every 6 hours Intravenous: 500–1000 mg every 6 hours	Onset: Oral: approximately 60 minutes Intravenous: 15 minutes Half-life: 2.4 hours	Metabolized in the liver by glucuronidation, sulfation, and oxidation via CYP2E1 to form a reactive metabolite NAPQI which is then metabolized to cysteine and mercapturic acid conjugates.	No	Scheduled doses may be more effective at opioid sparing than as-needed doses. Use with caution in patients with acute hepatic injury, cirrhosis, chronic alcohol use, and chronic malnutrition Intravenous acetaminophen has a faster onset, but no current evidence supports superiority of intravenous acetaminophen if patients can receive via alternative routes.

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Table 1. (*Continued*) Analgesia and Sedative Agent Key Characteristics.*

Agent	Typical Dose	Onset, Duration, Half-life	Pharmacokinetics, Metabolism, Elimination	Active Metabolite	Additional Considerations
Nonsteroidal anti-inflammatory drugs		Generally not preferred in the ICU setting unless the patient is at low risk for complications			
Gabapentin	Oral: 100–1200 mg every 8 hours Dose reductions required for renal dysfunction	Onset: 2–4 hours Half-life: 5–7 hours, directly proportional to creatinine clearance	Eliminated via renal excretion as unchanged drug	No	Most beneficial in patients experiencing neuropathic pain
Lidocaine	Intravenous load: 1–2 mg/kg Infusion: 1–2 mg/kg/hr	Onset: 1–2 minutes Offset: 20 minutes Lidocaine demonstrates reduced clearance and longer half-life with prolonged infusions	Complex hepatic metabolism via oxidative *N*-dealkylation by CYP1A2 and CYP3A4 yielding metabolites MEGX and GX (both active) as well as other inactive metabolites; Half-life is significantly prolonged in patients with hepatic impairment; With severe renal dysfunction, lidocaine clearance is reduced and accumulation of GX is increased.	Yes MEGX and GX	Narrow therapeutic index, early signs of toxicity typically neurologic in nature including delirium, tremor, tinnitus, and seizure. Severe toxicity may cause bradycardia and heart block. Contraindicated in patients with Stokes–Adams syndrome, Wolff–Parkinson–White syndrome, or severe SA, AV, or intraventricular block.
Sedatives — First line					
Propofol	Intravenous push: 10–50 mg every 30 minutes as needed Infusion: 5–50 μg/kg/min	Onset: 1–2 minutes Offset: variable with prolonged infusions	Hepatic conjugation to inactive metabolites which are renally excreted	No	May cause hypotension, particularly with high doses Provided as a lipid emulsion, monitor triglycerides at baseline and every 48–72 hours Propofol-related infusion syndrome: diagnosis of exclusion, presents as severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, renal failure, EKG changes, or cardiac failure Increased risk with prolonged infusions or high doses
Dexmedetomidine	Infusion: 0.2–1.5 μg/kg/hr	Onset: 30–60 minutes Half-life: 2 hours	Hepatic metabolism via glucuronidation and CYP2A6 aliphatic hydroxylation. Approximately 85% inactive metabolites are renally cleared within 24 hours.	No	May cause bradycardia, hypotension, and drug fevers. Bolus doses may increase risk for bradycardia. Maintains light sedation with limited impact on respiratory drive. Patients can develop tolerance and dependence with prolonged infusions.
Sedatives — Second Line					
Ketamine	Infusion sedative dosing: 5–30 μg/kg/min	Onset: 1 minute Offset: approximately 2 hours	Complex and extensive hepatic metabolism: CYP3A4, CYP2B6, CYP2C19 mediate *N*-demethylation into active metabolite norketamine.	Yes Norketamine	Emergence reactions may occur, typically with initiation/discontinuation and with periprocedural bolus doses. Use with caution in patient with psychiatric disorders Use with caution in patients with uncontrolled hypertension or tachycardia.

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Table 1. (*Continued*) Analgesia and Sedative Agent Key Characteristics.*

Agent	Typical Dose	Onset, Duration, Half-life	Pharmacokinetics, Metabolism, Elimination	Active Metabolite	Additional Considerations
Midazolam	Intravenous push: 2–4 mg every 30 min as needed Infusion: 1–4 mg/hr	Onset: approximately 3–5 minutes Duration: 2–4 hours (variable with prolonged infusions)	Hepatic metabolism via CYP3A4 to hydroxylated metabolites that are conjugated and excreted renally Highly lipophilic with increased accumulation in patients receiving longer durations or in morbidly obese patients	Yes α-hydroxymidazolam	Intermittent bolus doses are preferred to continuous infusions. Benzodiazepines may cause paradoxical agitation and delirium.
Lorazepam	Intravenous push: 1–4 mg every 30 minutes as needed	Onset: 15–20 minutes Duration: 6–8 hours	Hepatic metabolism via conjugation into inactive metabolites which are renally cleared	No	Intermittent bolus doses are preferred to continuous infusions. Benzodiazepines may cause paradoxical agitation and delirium. Intravenous formulation contains propylene glycol, monitor for toxicity with prolonged infusions including anion gap metabolic acidosis.

* AV denotes atrioventricular; CYP1A2, cytochrome P450 1A2; CYP2A6, cytochrome P450 2A6; CYP2B6, cytochrome P450 2B6; CYP2C19, cytochrome P450 2C19; CYP2E1, cytochrome P450 2E1; CYP3A4, cytochrome P450 3A4; EKG, electrocardiography; ICU, intensive care unit; M3G, morphine-3-glucoronide; M6G, morphine-6-glucuronide; NAPQI, *N*-acetyl-*p*-benzoquinone imine; SA, sinoatrial; MEGX, monoethylglycinexylidide; GX, glycinexylidide; and HM6G, hydromorphone-6-glucuronide.

potential adverse effects when choosing between propofol and dexmedetomidine.

Assess, Prevent, and Manage Delirium

Sedative selection can affect the risk of developing ICU delirium. Benzodiazepines should be avoided in favor of alternative agents.[2] Multicomponent bundles, such as ABCDEF, have been associated with a lower incidence of delirium.[8] Beyond sedative agent selection and use of multicomponent bundles, investigators have also evaluated the impact of other factors such as analgesic agent selection, RASS variability, sedative administration practices, and adjunctive agents on preventing and treating delirium.

A secondary analysis of the ANALGESIC trial evaluated the incidence of delirium in patients who received fentanyl versus morphine for analgosedation.[43] While the incidence of delirium was higher in the fentanyl group than in the morphine group, the 95% confidence interval around that estimate was wide and included the null. Interestingly, there was a linear association between the cumulative dose of opioid received and the use of antipsychotics, suggesting that higher cumulative doses of opioids may increase the likelihood of delirium.

Ritchie and colleagues performed a retrospective observational study and demonstrated that mechanically ventilated patients who developed delirium had a significantly higher coefficient of variation in RASS score than those without delirium.[44] There was no difference in mean RASS score and opioid and sedative total daily doses administered between the two groups. Although additional research is needed, results from this study may suggest that more consistent sedation levels may reduce the incidence of delirium.

Practices during the Covid-19 pandemic provided additional insight into the impact of sedation on delirium. Bernard-Valnet and colleagues performed a retrospective observational study and evaluated incidence of delirium in patients with ARDS and Covid-19 versus another etiologies.[45] Interestingly, there was no difference in incidence of delirium between the Covid-19 and other etiology groups despite higher total doses of propofol and fentanyl and longer durations of mechanical ventilation in the Covid-19 group. Use of sedative infusions was an independent predictor of delirium. Additionally, in a multinational retrospective observational study in critically ill patients with Covid-19, delirium was found to be present in over half of the study population (54.9%) with a median duration of 3 days.[24] Use of continuous benzodiazepine and opioid infusions was associated with delirium the next day. Results from these studies highlight the risk of delirium with benzodiazepines and also suggest that the use of other sedative and opioid infusions may also play a role.

Lastly, investigators have evaluated the utility of other medications such as antipsychotics and dexmedetomidine

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Table 2. Evidence for Specific Agents in Intensive Care Unit Sedation.*

Study Name (Year)	Study Medications	Number of Patients	Time in Goal Sedation	Delirium Prevalence	Time to Extubation	ICU Length of Stay	Mortality
Carson et al. (2006)[37]	Propofol versus lorazepam	132	No difference	N/A	5.8 days versus 8.4 days	Survivors: 8.6 days versus 12.7 days	Hospital: 25% versus 24%
MENDS (2007)[38]	Dexmedetomidine versus lorazepam	107	Time in stated goal 80% versus 67%	79% versus 82%	N/A	7.5 days versus 9 days	28 day: 17% versus 27%
SEDCOM (2009)[39]	Dexmedetomidine versus midazolam	366	Goal RASS −2 to 1 77.3% versus 75.1%	54% versus 76.6%	3.7 days versus 5.6 days	5.9 days versus 7.6 days	30 day: 22.5% versus 25.4%
MIDEX (2012)[40]	Dexmedetomidine versus midazolam	500	Excluded deep sedation 60.7% versus 56.6%	7.7% versus 10%	4.2 days versus 6.1 days	8.8 days versus 10.1 days	45 day: 27.3% versus 21.1%
PRODEX (2012)[40]	Dexmedetomidine versus propofol	498	Excluded deep sedation 64.6% versus 64.7%	4.9% versus 9.7%	2.9 days versus 3.9 days	6.8 days versus 7.7 days	45 day: 17.1% versus 19.4%
SPICE III (2019)[42]	Dexmedetomidine versus usual care (propofol or midazolam or combination)	3904	Goal RASS score −2 to 1 but deep sedation allowed as needed 56.6% versus 51.8%	40.7% versus 42.5%	3 days versus 3.3 days	6 days versus 6.3 days	90 day: 29.1% versus 29.1%
MENDS2 (2021)[41]	Dexmedetomidine versus propofol	432	Goal RASS score −2 to 0 57% versus 60%	Days alive without delirium 10.7 versus 10.8 days	3.8 days versus 4.9 days	6 days versus 7 days	90 day: 38% versus 39%

*ICU denotes intensive care unit; RASS, Richmond Agitation–Sedation Scale; and N/A, not applicable.

on treating and preventing delirium. In the MIND USA and AID ICU trials, antipsychotic agents administered to patients with delirium did not impact the duration of delirium or days alive and out of the hospital at 90 days.[46,47] Use of overnight dexmedetomidine in surgical patients has demonstrated promising results, with some studies showing a reduction in incidence of delirium.[48,49]

Although sedative agent selection and use of multicomponent bundles both play important roles in preventing delirium, other factors such as analgesic agent selection, RASS variability, and use of continuous infusion sedatives and opioids may also impact delirium outcomes. Additional research is needed in this area to solidify these potential relationships.

Early Mobility and Exercise

Results from initial early mobility and exercise studies demonstrated improved functional status at hospital discharge, shorter hospital and ICU length of stay, decreased ICU delirium days, increased ventilator-free days, and lower odds of readmission or death.[50-54] Investigators successfully and safely implemented early mobility protocols despite concurrent mechanical ventilation.[50,52-58] One key aspect to including mechanically ventilated patients in these protocols was the use of light sedation in which patients were able to follow commands.[50,54-56] Many investigators focused on initiating physical therapy once sedatives were discontinued.[54,56] Conversely, other investigators allowed patients to participate in early mobility protocols despite the need for sedatives, but coordinated these sessions around daily awakening trials or used passive cycling and range of motion.[51,55] More recent trials evaluating the impact of early mobility have failed to demonstrate similar positive outcomes.[57-59] A trial in mechanically ventilated patients found no difference in days alive and out of the hospital at 180 days between the early mobility and standard care groups.[57] There are many strengths of this trial, including that it was a prospective randomized trial comparing an individualized mobilization protocol to standard of care. One limitation is that authors state sedation was minimized to facilitate early mobilization, but do not provide specific details regarding weaning strategies. A high percentage of patients in the early mobility and usual care groups initially received continuous infusion sedatives and were deeply sedated (median RASS score −3 [interquartile range −4 to −2] vs. −3 [interquartile range −4 to −2], respectively). In the early mobility group, sedation was the primary barrier preventing participation in out-of-bed activities up to day 5. Additionally, over 60% of the study population had a lowest

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daily RASS score below −2 up to day 4. Although patients in the early mobility group had significantly longer mobilization sessions and were able to achieve higher levels of mobilization sooner, sedation practices may have still influenced the results. Kho and colleagues performed a randomized controlled trial in mechanically ventilated patients and compared in-bed cycling with usual physical therapy versus usual physical therapy alone.[58] There was no difference in Physical Function Test for ICU-scored between groups 3 days after ICU discharge. Patients were allowed to participate even if they were receiving continuous sedative infusions, and the trial protocol did not specify requirements for daily awakening trials. Cycle effort could be passive or was considered active if patient cycling rates exceeded the set ergometer speed with greater than zero watts of power for at least 2 minutes. More than 50% of precycling RASS scores were −5 to −2, which may have contributed to the low percentage of active cycling days (29.1%). It may be beneficial to integrate daily awakening trials with mobility activities to increase active patient involvement.

There are many barriers that influence patients' ability to participate in early mobility. Institutional barriers may include staffing shortages, lack of appropriate equipment, and limited physical and occupational therapy resources.[60,61] Kamdar and colleagues performed a secondary analysis of a prospective observational study and examined how patient-specific barriers impacted participation in daily physical therapy.[62] They demonstrated a negative association between use of sedative infusions and opioid boluses with physical therapy participation. The use of opioid boluses may be a marker of uncontrolled pain driving lack of participation rather than a direct medication effect. Additionally, these results demonstrate use of sedatives may drive lack of participation instead of mechanical ventilation. Similarly, Thomsen and colleagues performed a prospective pre- and postimplementation study and reported absence of sedative use was an independent predictor of increased ambulation in patients admitted to a respiratory ICU.[63] These studies support that limiting sedation can improve patient participation in early mobility and exercise.

Family Engagement and Empowerment

The F component of the ABCDEF bundle was introduced to ensure family engagement and empowerment was incorporated into the comprehensive care of patients in the ICU.[8] Compliance with this component is achieved if the patient or family participates in daily rounds or a family conference is held.[8,9] Implementation of this component was likely impacted by visitation restrictions during the Covid-19 pandemic, but family members should be reincorporated into care given the positive impact on outcomes such as delirium, ICU length of stay, and caregiver anxiety and depression.[64-67]

Limited evidence is available regarding family involvement and perceptions of sedation practices in mechanically ventilated patients. Prime and colleagues performed a prospective observational study and interviewed 16 awake, mechanically ventilated patients and their family members to better understand their experience during light sedation.[68] The questionnaire evaluated eight categories including preferences to be more awake. Fifty percent of patients agreed or strongly agreed that they preferred to be kept awake, and the mean score between patients and family members for this category was not significantly different. Beyond patient and family preference, there may be additional long-term benefits to the use of lighter sedation in regards to development of post-traumatic stress disorder in ICU survivors.[69]

Family members may also play a vital role in evaluating pain in critically ill patients. Puntillo and colleagues performed a prospective observational study of agreement in pain score assessments for noncomatose critically ill patients.[70] Agreement in pain intensity score between the patient and family was the highest, followed by the physician, and the nurse. The CPOT is one of the gold standard pain assessment scales used for patients who are unable to communicate.[1] Mohand-Saïd and colleagues performed a prospective observational study in which they enrolled 10 family members to evaluate pain using the CPOT after 15-minute training sessions.[71] Overall, all family members agreed or strongly agreed that they felt comfortable utilizing the CPOT and wanted to be more involved in pain assessments. Shahid and colleagues developed the CPOT-Fam in an effort to make the traditional CPOT more user friendly for family members in which the core components were reformatted into questions.[72] Accuracy of the CPOT-Fam was assessed prospectively by having recruited participants and investigators score sample cases, which demonstrated high agreement between evaluators.

Family members can play a critical role in optimizing analgesia and sedation practices in the ICU. Family presence may allow for patients to tolerate lighter sedation, and family members can assist with pain assessments and management for patients who are mechanically ventilated or unable to communicate. Investigators have evaluated risk factors

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for development of post-intensive care syndrome in family members, and demonstrated various patient, relative, and medical staff-related factors likely contribute.[73] Involving family members in analgesic and sedation decisions may help alleviate some of the medical staff-related factors such as communication and perceptions of care. Future studies are needed to better understand how to optimize the available sedation and pain scoring tools to incorporate family feedback and involvement.

Conclusions

Sedation practices are closely linked to ICU outcomes. Implementation of evidence-based strategies such as protocolized analgosedation and minimization of sedation to facilitate coordination of the ICU Liberation bundle should be promoted for all critically ill patients, as even small improvements in ventilator bundle compliance have demonstrated improvements in patient outcomes including duration of mechanical ventilation, ICU length of stay, delirium- and coma-free days, and hospital survival. Moving past the Covid-19 pandemic, hospitals should conduct evaluations of bundle compliance and develop strategies for continued process improvement, especially as they relate to analgesia- and sedative-based bundle components.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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